CLAIMS

1. Use of α-cyclodextrin or a derivative thereof for the preparation of a pharmaceutical composition for the oral administration of a LH-RH peptide analogue or one of its pharmaceutically acceptable salt.

2. Use according to claim 1 wherein said peptide analogue has the formula (SEQ ID N° : 1) :

A1-A2-A3-A4-A5-A6-A7-A8-Pro-Z (A)

in which :

- A1 is pGlu ; D-pGlu ; Sar ; AcSar ; Pro or a derivative thereof ; Ser ; D-Ser ; Ac-D-Ser ; Thr ; D-Thr ; Ac-D-Thr ; or an optionally substituted and/or acylated aromatic D-amino acid;

- A2 is a direct bond ; His ; or an optionally substituted aromatic D-amino acid;

- A3 is an optionally substituted aromatic L- or D-amino acid;

- A4 is Ala, Ser, D-Ser, MeSer, Ser(OBu^t), Ser(OBzl) or Thr;

- A5 is an optionally substituted aromatic L-amino acid or an optionally substituted basic L- or D-amino acid ;

- A6 is Gly ; (S)-spirolactam-Pro ; D-Pro ; D-Ser ; D-Thr ; D-Cys ; D-Met ; D-Asn ; D-Pen ; D-(S-Me)Pen ; D-(S-Et)Pen ; D-Ser(OBu^t) ; D-Asp(OBu^t) ; D-Glu(OBu^t) ; D-Thr(OBu^t) ; D-Cys(OBu^t) ; D-Ser(OR$_1$) where R$_1$ is a sugar moiety ; an aza-amino acid ; D-His which may be substituted on the imidazole ring by a (C_1-C_6)alkyl, a (C_2-C_7)acyl or a benzyl group ; an aliphatic D-amino acid with a (C_1-C_8)alkyl or a (C_3-C_6)cycloalkyl side chain ; an optionally substituted aromatic D-amino acid ; D-cyclohexadienyl-Gly ; D-perhydronaphthyl-Ala ; D-perhydrodiphenyl-Ala ; or an optionally substituted basic L- or D-amino acid;

- A7 is a linear, branched or cyclic aliphatic L-amino acid of 3 to 20 carbon atoms which may be N-alpha-substituted by a (C_1-C_4)alkyl group optionally substituted by one or several fluorine atoms ;

- A8 is an optionally substituted basic L- or D-amino acid;

- Z is GlyNH$_2$; D-AlaNH$_2$; azaGlyNH$_2$; or a group -NHR$_2$ where R$_2$ is a (C_1-C_4)alkyl which may be substituted by an hydroxy or one or several fluorine atoms ; a (C_3-C_6)cycloalkyl ; or a heterocyclic radical selected from morpholinyl, pyrrolidinyl and piperidyl.

3. Use according to claim 2 wherein said peptide analogue has the formula (SEQ ID N° : 2) :

A1-His-A3-A4-A5-A6-A7-A8-Pro-Z (I)

in which:

- A1 is pGlu, Sar or AcSar;
- A3 is an optionally substituted aromatic L-amino acid;
- A4 is Ala, Ser, D-Ser, MeSer, Ser(OBu^t), Ser(OBzl) or Thr;
- A5 is an optionally substituted aromatic L-amino acid ;
- A6 is Gly ; D-Pro ; (S)-spirolactam-Pro ; D-Ser ; D-Thr ; D-Cys ; D-Met ; D-Pen ; D-(S-Me)Pen ; D-(S-Et)Pen ; D-Ser(OBu^t) ; D-Asp(OBu^t) ; D-Glu(OBu^t) ; D-Thr(OBu^t) ; D-Cys(OBu^t) ; D-Ser(OR$_1$) where R$_1$ is a sugar moiety ; an aza-amino acid ; D-His which may be substituted on the imidazole ring by a (C_1-C_6)alkyl or a benzyl group ; an aliphatic D-amino acid with a (C_1-C_8)alkyl or a (C_3-C_6)cycloalkyl side chain ; an optionally substituted aromatic D-amino acid ; D-cyclohexadienyl-Gly ; D-perhydronaphtyl-Ala ; D-perhydrodiphenyl-Ala ; or an optionally substituted basic D-amino acid;
- A7 is a linear, branched or cyclic aliphatic L-amino acid of 3 to 20 carbon atoms which may be N-alpha-substituted by a (C_1-C_4)alkyl group optionally substituted by one or several fluorine atoms;
- A8 is an optionally substituted basic L-amino acid;
- Z is GlyNH$_2$; azaGlyNH$_2$; or a group -NHR$_2$ where R$_2$ is a (C_1-C_4)alkyl which may be substituted by an hydroxy or one or several fluorine atoms ; a (C_3-C_6)cycloalkyl ; or a heterocyclic radical selected from morpholinyl, pyrrolidinyl and piperidyl.

4. Use according to claim 3 wherein said peptide analogue has the formula (SEQ ID N° : 3) :

pGlu-His-A3-Ser-A5-A6-A7-Arg-Pro-Z (II)

in which A7 is Leu, Tle, Nle, Hol, Npg, Cha or Ada, which may be N-alpha-substituted by a methyl or ethyl group optionally substituted by one or several fluorine atoms.

5. Use according to claim 3 wherein said peptide analogue has the formula (SEQ ID N° : 4) :

pGlu-His-A3-Ser-A5-A6-A7-Arg-Pro-Z (III)

in which:

- A3 and A5 are each independently Phe, Tyr, Trp, 2MeTrp, HPhe, HTyr, Nal, 1Nal, Bal, Pal, 4Pal, or pClPhe ;

- A6 is (S)-spirolactam-Pro ; Gly; D-Pro ; D-Ser(OBu^t) ; D-Asp(OBu^t) ; D-Glu(OBu^t) ; D-Thr(OBu^t) ; D-Cys(OBu^t); D-His or D-His(Bzl) ; D-Ala, D-Leu, D-Tle, D-Nle, D-Hol, D-Npg or D-Cha ; D-Phe, D-HPhe, D-Tyr, D-HTyr, D-Trp, D-2MeTrp, D-Nal, D-1Nal, D-Bal, D-Pal, D-4Pal, or D-pClPhe; D-cyclohexadienyl-Gly ; D-perhydronaphtyl-Ala ; D-perhydrodiphenyl-Ala ; or D-APhe optionally substituted by an aminotriazolyl group ;

- A7 is Leu, Npg or Cha, which may be N-alpha-substituted by a methyl group;

- Z is $GlyNH_2$; $azaGlyNH_2$ or $-NC_2H_5$.

6. Use according to claim 3 wherein said peptide analogue has the formula (SEQ ID N° : 5) :

pGlu-His-Trp-Ser-Tyr-A6-A7-Arg-Pro-Z (IV)

in which:

- A6 is (S)-spirolactam-Pro, D-Leu, D-Ala, D-Nal, D-Phe, D-Ser(OBu^t) or D-Trp;

- A7 is Leu, MeLeu, Npg or MeNpg;

- Z is $GlyNH_2$; $azaGlyNH_2$ or $-NC_2H_5$.

7. Use according to one of claims 3 to 6 wherein the peptide analogue is selected from the group consisting of leuprorelin, [Npg^7]-leuprorelin, triptorelin, [Npg^7]-triptorelin, goserelin, [Npg^7]-goserelin, buserelin and [Npg^7]-buserelin.

8. Use according to claim 2 wherein said peptide analogue has the formula (SEQ ID N° : 6) :

A1-A2-A3-A4-A5-A6-A7-A8-Pro-Z (I')

in which:

- A1 is pGlu ; D-pGlu ; Sar ; AcSar ; Pro or a derivative thereof ; Ser ; D-Ser ; Ac-D-Ser ; Thr ; D-Thr ; Ac-D-Thr ; or an optionally substituted and/or acylated aromatic D-amino acid;

- A2 is a direct bond or an optionally substituted aromatic D-amino acid;

- A3 is an optionally substituted aromatic L- or D-amino acid;

- A4 is Ala, Ser, D-Ser, MeSer, Ser(OBu^t), Ser(OBzl) or Thr;

- A5 is an optionally substituted aromatic L-amino acid or an optionally substituted basic L- or D-amino acid;

- A6 is Gly ; (S)-spirolactam-Pro ; D-Pro ; D-Ser ; D-Thr ; D-Cys ; D-Met ; D-Asn ; D-Pen ; D-(S-Me)Pen ; D-(S-Et)Pen ; D-Ser(OBu^t) ; D-Asp(OBu^t) ; D-Glu(O-Bu^t) ; D-Thr(O-Bu^t) ; D-Cys(O-Bu^t) ; D-Ser(O-R_1) where R_1 is a sugar moiety ; an aliphatic D-amino acid with a (C_1-C_8)alkyl or a (C_3-C_6)cycloalkyl side chain ; an optionally substituted aromatic D-amino acid ; D-cyclohexadienyl-Gly ; D-perhydronaphthyl-Ala ; D-perhydrodiphenyl-Ala ; or an optionally substituted basic L- or D-amino acid;

- A7 is a linear, branched or cyclic aliphatic L-amino acid of 3 to 20 carbon atoms which may be N-alpha-substituted by a (C_1-C_4)alkyl group optionally substituted by one or several fluorine atoms;

- A8 is an optionally substituted basic L- or D-amino acid;

- Z is GlyNH$_2$ or D-AlaNH$_2$.

9. Use according to claim 8 wherein the peptide analogue has the formula (SEQ ID N° : 7):

Ac-D-Nal-D-pClPhe-D-Pal-Ser-A5-A6-A7-A8-Pro-D-AlaNH$_2$ (II')

in which :

- A5 is Tyr, HTyr, MeTyr, MeHTyr, NicLys or IprLys;

- A6 is (S)-spirolactam-Pro, D-Arg, D-NicLys, D-IprLys, D-Cit, D-HCit or D-Asn;

- A7 is Leu, MeLeu, Npg or MeNpg;

- A8 is Arg, NicLys or IprLys.

10. Use according to claim 8 or 9 wherein the peptide analogue is selected from the group consisting of antide, [Npg^7]-antide, cetrorelix, [Npg^7]-cetrorelix, abarelix and [Npg^7]-abarelix.

11. Use according to one of claims 1 to 10 wherein the α-cyclodextrin derivative is selected from the group consisting of methylated α-cyclodextrin, hexakis(2,3,6-tri-O-methyl)-α-cyclodextrin, carboxymethylated α-cyclodextrin and phosphated α-cyclodextrin.

12. Use according to one of claims 1 to 11 of α-cyclodextrin or hexakis(2,3,6-tri-O-methyl)-α-cyclodextrin.

13. Use according to one of claims 1 to 12 wherein the pharmaceutical composition is intended to be delivered to the gastrointestinal tract.

14. Use according to one of claims 1 to 13 wherein the pharmaceutical composition is intended for the treatment of infertility, hypogonadic or hypergonadic states.

15. Use according to one of claims 1 to 13 wherein the pharmaceutical composition is a contraceptive agent.

16. Use according to one of claims 1 to 13 wherein the pharmaceutical composition is intended for the treatment or prevention of prostate cancer or benign prostatic hypertrophy.

17. Use according to one of claims 1 to 13 wherein the pharmaceutical composition is intended for the treatment or prevention of breast cancer.

18. Use according to one of claims 1 to 13 wherein the pharmaceutical composition is intended for the treatment or prevention of sex hormone-related benign or malignant tumors.

19. Use according to one of claims 1 to 13 wherein the pharmaceutical composition is intended for the treatment or prevention of sex hormone-independent but LH-RH sensitive benign or malignant tumors.

20. Use according to one of claims 1 to 13 wherein the pharmaceutical composition is intended for the treatment or prevention of benign or malignant lymphoproliferative disorders.

21. A pharmaceutical composition for the gastrointestinal delivery by oral administration of a LH-RH peptide analogue which comprises a therapeutically effective amount of said peptide analogue in combination with α-cyclodextrin or a derivative thereof.

22. The pharmaceutical composition according to claim 21 which further comprises excipients suitable for the gastrointestinal delivery of the peptide analogue.

Sub A2

23. The pharmaceutical composition according to claim 21 or 22 wherein said peptide analogue has the formula (SEQ ID N° : 1) :

A1-A2-A3-A4-A5-A6-A7-A8-Pro-Z (A)

in which :

- A1 is pGlu ; D-pGlu ; Sar ; AcSar ; Pro or a derivative thereof ; Ser ; D-Ser ; Ac-D-Ser ; Thr ; D-Thr ; Ac-D-Thr ; or an optionally substituted and/or acylated aromatic D-amino acid;

- A2 is a direct bond ; His ; or an optionally substituted aromatic D-amino acid;

Sub A2

- A3 is an optionally substituted aromatic L- or D-amino acid;

- A4 is Ala, Ser, D-Ser, MeSer, Ser(OBu^t), Ser(OBzl) or Thr;

- A5 is an optionally substituted aromatic L-amino acid or an optionally substituted basic L- or D-amino acid;

- A6 is Gly ; (S)-spirolactam-Pro ; D-Pro ; D-Ser ; D-Thr ; D-Cys ; D-Met ; D-Asn ; D-Pen ; D-(S-Me)Pen ; D-(S-Et)Pen ; D-Ser(OBu^t) ; D-Asp(OBu^t) ; D-Glu(OBu^t) ; D-Thr(OBu^t) ; D-Cys(OBu^t) ; D-Ser(OR$_1$) where R$_1$ is a sugar moiety ; an aza-amino acid ; D-His which may be substituted on the imidazole ring by a (C_1-C_6)alkyl, a (C_2-C_7)acyl or a benzyl group ; an aliphatic D-amino acid with a (C_1-C_8)alkyl or a (C_3-C_6)cycloalkyl side chain ; an optionally substituted aromatic D-amino acid ; D-cyclohexadienyl-Gly ; D-perhydronaphthyl-Ala ; D-perhydrodiphenyl-Ala ; or an optionally substituted basic L- or D-amino acid;

- A7 is a linear, branched or cyclic aliphatic L-amino acid of 3 to 20 carbon atoms which may be N-alpha-substituted by a (C_1-C_4)alkyl group optionally substituted by one or several fluorine atoms;

- A8 is an optionally substituted basic L- or D-amino acid;

- Z is GlyNH$_2$; D-AlaNH$_2$; azaGlyNH$_2$; or a group -NHR$_2$ where R$_2$ is a (C_1-C_4)alkyl which may be substituted by an hydroxy or one or several fluorine atoms ; a (C_3-C_6)cycloalkyl ; or a heterocyclic radical selected from morpholinyl, pyrrolidinyl and piperidyl.

24. The pharmaceutical composition according to claim 23 wherein said peptide analogue has the formula (SEQ ID N° : 2) :

A1-His-A3-A4-A5-A6-A7-A8-Pro-Z (I)

in which:

- A1 is pGlu, Sar or AcSar;

- A3 is an optionally substituted aromatic L-amino acid ;

- A4 is Ala, Ser, D-Ser, MeSer, Ser(OBu^t), Ser(OBzl) or Thr;

- A5 is an optionally substituted aromatic L-amino acid ;

- A6 is Gly ; D-Pro ; (S)-spirolactam-Pro ; D-Ser ; D-Thr ; D-Cys ; D-Met ; D-Pen ; D-(S-Me)Pen ; D-(S-Et)Pen ; D-Ser(OBu^t) ; D-Asp(OBu^t) ; D-Glu(OBu^t) ; D-Thr(OBu^t) ; D-Cys(OBu^t) ; D-Ser(OR$_1$) where R$_1$ is a sugar moiety ; an aza-amino acid ; D-His which may be substituted on the imidazole ring by a (C_1-C_6)alkyl or a benzyl group ; an aliphatic D-amino acid with a (C_1-C_8)alkyl or a (C_3-C_6)cycloalkyl side chain ; an optionally substituted aromatic D-amino acid ; D-cyclohexadienyl-Gly ;

D-perhydronaphtyl-Ala ; D-perhydrodiphenyl-Ala ; or an optionally substituted basic D-amino acid ;

- A7 is a linear, branched or cyclic aliphatic L-amino acid of 3 to 20 carbon atoms which may be N-alpha-substituted by a (C_1-C_4)alkyl group optionally substituted by one or several fluorine atoms;

- A8 is an optionally substituted basic L-amino acid;

- Z is $GlyNH_2$; $azaGlyNH_2$; or a group $-NHR_2$ where R_2 is a (C_1-C_4)alkyl which may be substituted by an hydroxy or one or several fluorine atoms ; a (C_3-C_6)cycloalkyl ; or a heterocyclic radical selected from morpholinyl, pyrrolidinyl and piperidyl.

25. The pharmaceutical composition according to claim 24 wherein said peptide analogue has the formula (SEQ ID N° : 3) :

pGlu-His-A3-Ser-A5-A6-A7-Arg-Pro-Z (II)

in which A7 is Leu, Tle, Nle, Hol, Npg, Cha or Ada, which may be N-alpha-substituted by a methyl or ethyl group optionally substituted by one or several fluorine atoms.

26. The pharmaceutical composition according to claim 24 wherein said peptide analogue has the formula (SEQ ID N° : 4) :

pGlu-His-A3-Ser-A5-A6-A7-Arg-Pro-Z (III)

in which:

- A3 and A5 are each independently Phe, Tyr, Trp, 2MeTrp, HPhe, HTyr, Nal, 1Nal, Bal, Pal, 4Pal, or pClPhe ;

- A6 is (S)-spirolactam-Pro ; Gly; D-Pro ; D-Ser(OBu^t) ; D-Asp(OBu^t) ; D-Glu(OBu^t) ; D-Thr(OBu^t) ; D-Cys(OBu^t); D-His or D-His(Bzl) ; D-Ala, D-Leu, D-Tle, D-Nle, D-Hol, D-Npg or D-Cha ; D-Phe, D-HPhe, D-Tyr, D-HTyr, D-Trp, D-2MeTrp, D-Nal, D-1Nal, D-Bal, D-Pal, D-4Pal, or D-pClPhe; D-cyclohexadienyl-Gly ; D-perhydronaphtyl-Ala ; D-perhydrodiphenyl-Ala or D-APhe optionally substituted by an aminotriazolyl group;

- A7 is Leu, Npg or Cha, which may be N-alpha-substituted by a methyl group;

- Z is $GlyNH_2$, $azaGlyNH_2$ or $-NC_2H_5$.

27. The pharmaceutical composition according to claim 24 wherein said peptide analogue has the formula (SEQ ID N° : 5) :

pGlu-His-Trp-Ser-Tyr-A6-A7-Arg-Pro-Z (IV)

in which:

- A6 is (S)-spirolactam-Pro, D-Leu, D-Ala, D-Nal, D-Phe, D-Ser(OBu^t) or D-Trp;

- A7 is Leu, MeLeu, Npg or MeNpg;

- Z is GlyNH$_2$, azaGlyNH$_2$ or -NC$_2$H$_5$.

28. The pharmaceutical composition according to one of claims 24 to 27 wherein the peptide analogue is selected from the group consisting of leuprorelin, [Npg^7]-leuprorelin, triptorelin, [Npg^7]-triptorelin, goserelin, [Npg^7]-goserelin, buserelin and [Npg^7]-buserelin.

29. The pharmaceutical composition according to claim 23 wherein said peptide analogue has the formula (SEQ ID N° : 6) :

A1-A2-A3-A4-A5-A6-A7-A8-Pro-Z (I')

in which:

- A1 is pGlu ; D-pGlu ; Sar ; AcSar ; Pro or a derivative thereof ; Ser ; D-Ser ; Ac-D-Ser ; Thr ; D-Thr ; Ac-D-Thr ; or an optionally substituted and/or acylated aromatic D-amino acid;

- A2 is a direct bond or an optionally substituted aromatic D-amino acid;

- A3 is an optionally substituted aromatic L- or D-amino acid;

- A4 is Ala, Ser, D-Ser, MeSer, Ser(OBu^t), Ser(OBzl) or Thr;

- A5 is an optionally substituted aromatic L-amino acid or an optionally substituted basic L- or D-amino acid;

- A6 is Gly ; (S)-spirolactam-Pro ; D-Pro ; D-Ser ; D-Thr ; D-Cys ; D-Met ; D-Asn ; D-Pen ; D-(S-Me)Pen ; D-(S-Et)Pen ; D-Ser(OBu^t) ; D-Asp(OBu^t) ; D-Glu(O-Bu^t) ; D-Thr(O-Bu^t) ; D-Cys(O-Bu^t) ; D-Ser(O-R$_1$) where R$_1$ is a sugar moiety ; an aliphatic D-amino acid with a (C$_1$-C$_8$)alkyl or a (C$_3$-C$_6$)cycloalkyl side chain ; an optionally substituted aromatic D-amino acid ; D-cyclohexadienyl-Gly ; D-perhydronaphthyl-Ala ; D-perhydrodiphenyl-Ala ; or an optionally substituted basic L- or D-amino acid;

- A7 is a linear, branched or cyclic aliphatic L-amino acid of 3 to 20 carbon atoms which may be N-alpha-substituted by a (C$_1$-C$_4$)alkyl group optionally substituted by one or several fluorine atoms;

- A8 is an optionally substituted basic L- or D-amino acid;

- Z is GlyNH$_2$ or D-AlaNH$_2$.

30. The pharmaceutical composition according to claim 29 wherein the peptide analogue has the formula (SEQ ID N° : 7):

Ac-D-Nal-D-pClPhe-D-Pal-Ser-A5-A6-A7-A8-Pro-D-AlaNH$_2$ (II')

in which :

- A5 is Tyr, HTyr, MeTyr, MeHTyr, NicLys or IprLys;
- A6 is (S)-spirolactam-Pro, D-Arg, D-NicLys, D-IprLys, D-Cit, D-HCit or D-Asn;
- A7 is Leu, MeLeu, Npg or MeNpg;
- A8 is Arg, NicLys or IprLys.

Sub A4

31. The pharmaceutical composition according to claim 29 or 30 wherein the peptide analogue is selected from the group consisting of antide, [Npg^7]-antide, cetrorelix, [Npg^7]-cetrorelix, abarelix and [Npg^7]-abarelix.

32. The pharmaceutical composition according to one of claims 21 to 31 wherein the α-cyclodextrin derivative is selected from the group consisting of methylated α-cyclodextrin, hexakis(2,3,6-tri-O-methyl)-α-cyclodextrin, carboxymethylated α-cyclodextrin and phosphated α-cyclodextrin.

33. The pharmaceutical composition according to one of claims 21 to 32 comprising α-cyclodextrin or hexakis(2,3,6-tri-O-methyl)-α-cyclodextrin in combination with the LH-RH peptide analogue.

34. The pharmaceutical composition according to one of claims 21 to 33 which further comprises a protease inhibitor and/or an absorption enhancer.

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32. The pharmaceutical composition according to one of claims 21 to 31 wherein the α-cyclodextrin derivative is selected from the group consisting of methylated α-cyclodextrin, hexakis(2,3,6-tri-O-methyl)-α-cyclodextrin, carboxymethylated α-cyclodextrin and phosphated α-cyclodextrin.

33. The pharmaceutical composition according to claim 32 wherein the α-cyclodextrin derivative is hexakis(2,3,6-tri-O-methyl)-α-cyclodextrin.

34. The pharmaceutical composition according to one of claims 21 to 33 which further comprises a protease inhibitor and/or an absorption enhancer.

Added

P2 lines 3-4

35. A method of enhancing the biological activity of a LH-RH peptide analogue which comprises orally administering to a patient in need thereof a therapeutically effective amount of said analogue in combination with α-cyclodextrin or a derivative thereof.

36. The method according to claim 35, wherein said peptide analogue has the formula (SEQ ID N° : 1) :

A1-A2-A3-A4-A5-A6-A7-A8-Pro-Z (A)

in which :

- A1 is pGlu ; D-pGlu ; Sar ; AcSar ; Pro or a derivative thereof ; Ser ; D-Ser ; Ac-D-Ser ; Thr ; D-Thr ; Ac-D-Thr ; or an aromatic D-amino acid which may be acylated;
- A2 is a direct bond ; His ; or an aromatic D-amino acid;
- A3 is an aromatic L- or D-amino acid;
- A4 is Ala, Ser, D-Ser, MeSer, Ser(OBu^t), Ser(OBzl) or Thr;
- A5 is an aromatic L-amino acid or a basic L- or D-amino acid ;
- A6 is Gly ; (S)-spirolactam-Pro ; D-Pro ; D-Ser ; D-Thr ; D-Cys ; D-Met ; D-Asn ; D-Pen ; D-(S-Me)Pen ; D-(S-Et)Pen ; D-Ser(OBu^t) ; D-Asp(OBu^t) ; D-Glu(OBu^t) ; D-Thr(OBu^t) ; D-Cys(OBu^t) ; D-Ser(OR$_1$) where R$_1$ is a sugar moiety ; an aza-amino acid ; D-His which may be substituted on the imidazole ring by a (C$_1$-C$_6$)alkyl, a (C$_2$-C$_7$)acyl or a benzyl group ; an aliphatic D-amino acid with a (C$_1$-C$_6$)alkyl or a (C$_3$-C$_6$)cycloalkyl side chain ; an aromatic D-amino acid ; D-cyclohexadienyl-Gly ; D-perhydronaphthyl-Ala ; D-perhydrodiphenyl-Ala ; or a basic L- or D-amino acid;
- A7 is a linear, branched or cyclic aliphatic L-amino acid of 3 to 20 carbon atoms which may be N-alpha-substituted by a (C$_1$-C$_4$)alkyl group optionally substituted by one or several fluorine atoms ;
- A8 is a basic L- or D-amino acid;
- Z is GlyNH$_2$; D-AlaNH$_2$; azaGlyNH$_2$; or a group -NHR$_2$ where R$_2$ is a (C$_1$-C$_4$)alkyl which may be substituted by an hydroxy or one or several fluorine atoms ; a (C$_3$-C$_6$)cycloalkyl ; or a heterocyclic radical selected from morpholinyl, pyrrolidinyl and piperidyl.

37. The method according to claim 36 wherein said peptide analogue has the formula (SEQ ID N° : 2) :

A1-His-A3-A4-A5-A6-A7-A8-Pro-Z (I)

in which:

- A1 is pGlu, Sar or AcSar;
- A3 is an aromatic L-amino acid;
- A4 is Ala, Ser, D-Ser, MeSer, Ser(OBu^t), Ser(OBzl) or Thr;
- A5 is an aromatic L-amino acid ;
- A6 is Gly ; D-Pro ; (S)-spirolactam-Pro ; D-Ser ; D-Thr ; D-Cys ; D-Met ; D-Pen ; D-(S-Me)Pen ; D-(S-Et)Pen ; D-Ser(OBu^t) ; D-Asp(OBu^t) ; D-Glu(OBu^t) ; D-Thr(OBu^t) ; D-Cys(OBu^t) ; D-Ser(OR$_1$) where R$_1$ is a sugar moiety ; an aza-amino acid ; D-His which may be substituted on the imidazole ring by a (C_1-C_6)alkyl or a benzyl group ; an aliphatic D-amino acid with a (C_1-C_8)alkyl or a (C_3-C_6)cycloalkyl side chain ; an aromatic D-amino acid ; D-cyclohexadienyl-Gly ; D-perhydronaphtyl-Ala ; D-perhydrodiphenyl-Ala ; or a basic D-amino acid;
- A7 is a linear, branched or cyclic aliphatic L-amino acid of 3 to 20 carbon atoms which may be N-alpha-substituted by a (C_1-C_4)alkyl group optionally substituted by one or several fluorine atoms;
- A8 is a basic L-amino acid;
- Z is GlyNH$_2$; azaGlyNH$_2$; or a group -NHR$_2$ where R$_2$ is a (C_1-C_4)alkyl which may be substituted by an hydroxy or one or several fluorine atoms ; a (C_3-C_6)cycloalkyl ; or a heterocyclic radical selected from morpholinyl, pyrrolidinyl and piperidyl.

38. The method according to claim 37 wherein said peptide analogue has the formula (SEQ ID N° : 3) :

pGlu-His-A3-Ser-A5-A6-A7-Arg-Pro-Z (II)

in which A7 is Leu, Tle, Nle, Hol, Npg, Cha or Ada, which may be N-alpha-substituted by a methyl or ethyl group optionally substituted by one or several fluorine atoms.

39. The method according to claim 37 wherein said peptide analogue has the formula (SEQ ID N° : 4) :

pGlu-His-A3-Ser-A5-A6-A7-Arg-Pro-Z (III)

in which:

- A3 and A5 are each independently Phe, Tyr, Trp, 2MeTrp, HPhe, HTyr, Nal, 1Nal, Bal, Pal, 4Pal, or pClPhe ;
- A6 is (S)-spirolactam-Pro ; Gly; D-Pro ; D-Ser(OBu^t) ; D-Asp(OBu^t) ; D-Glu(OBu^t) ; D-Thr(OBu^t) ; D-Cys(OBu^t); D-His or D-His(Bzl) ; D-Ala, D-Leu, D-Tle, D-Nle, D-Hol, D-Npg or

D-Cha ; D-Phe, D-HPhe, D-Tyr, D-HTyr, D-Trp, D-2MeTrp, D-Nal, D-1Nal, D-Bal, D-Pal, D-4Pal, or D-pClPhe; D-cyclohexadienyl-Gly ; D-perhydronaphtyl-Ala ; D-perhydrodiphenyl-Ala ; or D-APhe optionally substituted by an aminotriazolyl group ;

- A7 is Leu, Npg or Cha, which may be N-alpha-substituted by a methyl group;
- Z is $GlyNH_2$; $azaGlyNH_2$ or $-NC_2H_5$.

40. The method according to claim 37 wherein said peptide analogue has the formula (SEQ ID N° : 5) :

pGlu-His-Trp-Ser-Tyr-A6-A7-Arg-Pro-Z (IV)

in which:

- A6 is (S)-spirolactam-Pro, D-Leu, D-Ala, D-Nal, D-Phe, D-Ser(OBu^t) or D-Trp;
- A7 is Leu, MeLeu, Npg or MeNpg;
- Z is $GlyNH_2$; $azaGlyNH_2$ or $-NC_2H_5$.

41. The method according to one of claims 37 to 40 wherein the peptide analogue is selected from the group consisting of leuprorelin, [Npg^7]-leuprorelin, triptorelin, [Npg^7]-triptorelin, goserelin, [Npg^7]-goserelin, buserelin and [Npg^7]-buserelin.

SubA5

42. The method according to claim 36 wherein said peptide analogue has the formula (SEQ ID N° : 6) :

A1-A2-A3-A4-A5-A6-A7-A8-Pro-Z (I')

in which:

- A1 is pGlu ; D-pGlu ; Sar ; AcSar ; Pro or a derivative thereof ; Ser ; D-Ser ; Ac-D-Ser ; Thr ; D-Thr ; Ac-D-Thr ; or an aromatic D-amino acid which may be acylated;
- A2 is a direct bond or an aromatic D-amino acid;
- A3 is an aromatic L- or D-amino acid;
- A4 is Ala, Ser, D-Ser, MeSer, Ser(OBu^t), Ser(OBzl) or Thr;
- A5 is an aromatic L-amino acid or a basic L- or D-amino acid;
- A6 is Gly ; D-Pro ; D-Ser ; D-Thr ; D-Cys ; D-Met ; D-Asn ; D-Pen ; D-(S-Me)Pen ; D-(S-Et)Pen ; D-Ser(OBu^t) ; D-Asp(OBu^t) ; D-Glu(O-Bu^t) ; D-Thr(O-Bu^t) ; D-Cys(O-Bu^t) ; D-Ser(O-R_1) where R_1 is a sugar moiety ; an aliphatic D-amino acid with a (C_1-C_8)alkyl or a (C_3-C_6)cycloalkyl side chain ; an aromatic D-amino acid ; D-cyclohexadienyl-Gly ; D-perhydronaphthyl-Ala ; D-perhydrodiphenyl-Ala ; or a basic L- or D-amino acid;
- A7 is a linear, branched or cyclic aliphatic L-amino acid of 3 to 20 carbon atoms which may be N-alpha-substituted by a (C_1-C_4)alkyl group optionally substituted by one or several fluorine atoms;
- A8 is a basic L- or D-amino acid;

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- Z is $GlyNH_2$ or $D\text{-}AlaNH_2$.

43. The method according to claim 42 wherein the peptide analogue has the formula (SEQ ID N° : 7):

Ac-D-Nal-D-pClPhe-D-Pal-Ser-A5-A6-A7-A8-Pro-$D\text{-}AlaNH_2$ (II')

in which :

- A5 is Tyr, HTyr, MeTyr, MeHTyr, NicLys or IprLys;
- A6 is (S)spirolactam-Pro, D-Arg, D-NicLys, D-IprLys, D-Cit, D-HCit or D-Asn;
- A7 is Leu, MeLeu, Npg or MeNpg;
- A8 is Arg, NicLys or IprLys.

44. The method according to claim 42 or 43 wherein the peptide analogue is selected from the group consisting of antide, [Npg^7]-antide, cetrorelix, [Npg^7]-cetrorelix, abarelix and [Npg^7]-abarelix.

45. The method according to one of claims 35 to 44 wherein the α-cyclodextrin derivative is selected from the group consisting of methylated α-cyclodextrin, hexakis(2,3,6-tri-O-methyl)-α-cyclodextrin, carboxymethylated α-cyclodextrin and phosphated α-cyclodextrin.

46. The method according to claim 45 wherein the α-cyclodextrin derivative is hexakis(2,3,6-tri-O-methyl)-α-cyclodextrin.

47. A method of treating a disease wherein a LH-RH agonist or antagonist action is required which comprises orally administering to a patient in need thereof a therapeutically effective amount of a LH-RH peptide analogue in combination with α-cyclodextrin or a derivative thereof, wherein said peptide analogue has the formula (SEQ ID N° : 1) :

A1-A2-A3-A4-A5-A6-A7-A8-Pro-Z (A)

in which :

- A1 is pGlu ; D-pGlu ; Sar ; AcSar ; Pro or a derivative thereof ; Ser ; D-Ser ; Ac-D-Ser ; Thr ; D-Thr ; Ac-D-Thr ; or an aromatic D-amino acid which may be acylated;
- A2 is a direct bond ; His ; or an aromatic D-amino acid;
- A3 is an aromatic L- or D-amino acid;
- A4 is Ala, Ser, D-Ser, MeSer, Ser(OBu^t), Ser(OBzl) or Thr;
- A5 is an aromatic L-amino acid or a basic L- or D-amino acid ;
- A6 is Gly ; (S)-spirolactam-Pro ; D-Pro ; D-Ser ; D-Thr ; D-Cys ; D-Met ; D-Asn ; D-Pen ; D-(S-Me)Pen ; D-(S-Et)Pen ; D-Ser(OBu^t) ; D-Asp(OBu^t) ; D-Glu(OBu^t) ; D-Thr(OBu^t) ; D-Cys(OBu^t) ; D-Ser(OR_1) where R_1 is a sugar moiety ; an aza-amino acid ; D-His which may be substituted on the imidazole ring by a (C_1-C_6)alkyl, a (C_2-C_7)acyl or a benzyl group ; an aliphatic D-amino acid with a (C_1-C_8)alkyl or a (C_3-C_8)cycloalkyl side chain ; an aromatic D-

amino acid ; D-cyclohexadienyl-Gly ; D-perhydronaphthyl-Ala ; D-perhydrodiphenyl-Ala ; or a basic L- or D-amino acid;

- A7 is a linear, branched or cyclic aliphatic L-amino acid of 3 to 20 carbon atoms which may be N-alpha-substituted by a (C_1-C_4)alkyl group optionally substituted by one or several fluorine atoms ;
- A8 is a basic L- or D-amino acid;
- Z is $GlyNH_2$; $D\text{-}AlaNH_2$; $azaGlyNH_2$; or a group $-NHR_2$ where R_2 is a (C_1-C_4)alkyl which may be substituted by an hydroxy or one or several fluorine atoms ; a (C_3-C_6)cycloalkyl ; or a heterocyclic radical selected from morpholinyl, pyrrolidinyl and piperidyl.

48. The method according to claim 47 wherein said peptide analogue has the formula (SEQ ID N° : 2) :

A1-His-A3-A4-A5-A6-A7-A8-Pro-Z (I)

in which:

- A1 is pGlu, Sar or AcSar;
- A3 is an aromatic L-amino acid;
- A4 is Ala, Ser, D-Ser, MeSer, Ser(OBu^t), Ser(OBzl) or Thr;
- A5 is an aromatic L-amino acid ;
- A6 is Gly ; D-Pro ; (S)-spirolactam-Pro ; D-Ser ; D-Thr ; D-Cys ; D-Met ; D-Pen ; D-(S-Me)Pen ; D-(S-Et)Pen ; D-Ser(OBu^t) ; D-Asp(OBu^t) ; D-Glu(OBu^t) ; D-Thr(OBu^t) ; D-Cys(OBu^t) ; D-Ser(OR_1) where R_1 is a sugar moiety ; an aza-amino acid ; D-His which may be substituted on the imidazole ring by a (C_1-C_6)alkyl or a benzyl group ; an aliphatic D-amino acid with a (C_1-C_6)alkyl or a (C_3-C_6)cycloalkyl side chain ; an aromatic D-amino acid ; D-cyclohexadienyl-Gly ; D-perhydronaphtyl-Ala ; D-perhydrodiphenyl-Ala ; or a basic D-amino acid;
- A7 is a linear, branched or cyclic aliphatic L-amino acid of 3 to 20 carbon atoms which may be N-alpha-substituted by a (C_1-C_4)alkyl group optionally substituted by one or several fluorine atoms;
- A8 is a basic L-amino acid;
- Z is $GlyNH_2$; $azaGlyNH_2$; or a group $-NHR_2$ where R_2 is a (C_1-C_4)alkyl which may be substituted by an hydroxy or one or several fluorine atoms ; a (C_3-C_6)cycloalkyl ; or a heterocyclic radical selected from morpholinyl, pyrrolidinyl and piperidyl.

49. The method according to claim 48 wherein said peptide analogue has the formula (SEQ ID N° : 3) :

pGlu-His-A3-Ser-A5-A6-A7-Arg-Pro-Z (II)

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in which A7 is Leu, Tle, Nle, Hol, Npg, Cha or Ada, which may be N-alpha-substituted by a methyl or ethyl group optionally substituted by one or several fluorine atoms.

50. The method according to claim 48 wherein said peptide analogue has the formula (SEQ ID N° : 4) :

pGlu-His-A3-Ser-A5-A6-A7-Arg-Pro-Z (III)

in which:

- A3 and A5 are each independently Phe, Tyr, Trp, 2MeTrp, HPhe, HTyr, Nal, 1Nal, Bal, Pal, 4Pal, or pClPhe ;
- A6 is (S)-spirolactam-Pro ; Gly; D-Pro ; D-Ser(OBu^t) ; D-Asp(OBu^t) ; D-Glu(OBu^t) ; D-Thr(OBu^t) ; D-Cys(OBu^t); D-His or D-His(Bzl) ; D-Ala, D-Leu, D-Tle, D-Nle, D-Hol, D-Npg or D-Cha ; D-Phe, D-HPhe, D-Tyr, D-HTyr, D-Trp, D-2MeTrp, D-Nal, D-1Nal, D-Bal, D-Pal, D-4Pal, or D-pClPhe; D-cyclohexadienyl-Gly ; D-perhydronaphtyl-Ala ; D-perhydrodiphenyl-Ala ; or D-APhe optionally substituted by an aminotriazolyl group ;
- A7 is Leu, Npg or Cha, which may be N-alpha-substituted by a methyl group;
- Z is $GlyNH_2$; $azaGlyNH_2$ or $-NC_2H_5$.

51. The method according to claim 48 wherein said peptide analogue has the formula (SEQ ID N° : 5) :

pGlu-His-Trp-Ser-Tyr-A6-A7-Arg-Pro-Z (IV)

in which:

- A6 is (S)-spirolactam-Pro, D-Leu, D-Ala, D-Nal, D-Phe, D-Ser(OBu^t) or D-Trp;
- A7 is Leu, MeLeu, Npg or MeNpg;
- Z is $GlyNH_2$; $azaGlyNH_2$ or $-NC_2H_5$.

52. The method according to one of claims 48 to 51 wherein the peptide analogue is selected from the group consisting of leuprorelin, [Npg^7]-leuprorelin, triptorelin, [Npg^7]-triptorelin, goserelin, [Npg^7]-goserelin, buserelin and [Npg^7]-buserelin.

Sub A7

53. The method according to claim 47 wherein said peptide analogue has the formula (SEQ ID N° : 6) :

A1-A2-A3-A4-A5-A6-A7-A8-Pro-Z (I')

in which:

- A1 is pGlu ; D-pGlu ; Sar ; AcSar ; Pro or a derivative thereof ; Ser ; D-Ser ; Ac-D-Ser ; Thr ; D-Thr ; Ac-D-Thr ; or an aromatic D-amino acid which may be acylated;
- A2 is a direct bond or an aromatic D-amino acid;
- A3 is an aromatic L- or D-amino acid;
- A4 is Ala, Ser, D-Ser, MeSer, Ser(OBu^t), Ser(OBzl) or Thr;

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- A5 is an aromatic L-amino acid or a basic L- or D-amino acid;
- A6 is Gly ; D-Pro ; D-Ser ; D-Thr ; D-Cys ; D-Met ; D-Asn ; D-Pen ; D-(S-Me)Pen ; D-(S-Et)Pen ; D-Ser(OBu^t) ; D-Asp(OBu^t) ; D-Glu(O-Bu^t) ; D-Thr(O-Bu^t) ; D-Cys(O-Bu^t) ; D-Ser(O-R_1) where R_1 is a sugar moiety ; an aliphatic D-amino acid with a (C_1-C_8)alkyl or a (C_3-C_6)cycloalkyl side chain ; an aromatic D-amino acid ; D-cyclohexadienyl-Gly ; D-perhydronaphthyl-Ala ; D-perhydrodiphenyl-Ala ; or a basic L- or D-amino acid;
- A7 is a linear, branched or cyclic aliphatic L-amino acid of 3 to 20 carbon atoms which may be N-alpha-substituted by a (C_1-C_4)alkyl group optionally substituted by one or several fluorine atoms;
- A8 is a basic L- or D-amino acid;
- Z is GlyNH_2 or D-AlaNH_2.

54. The method according to claim 53 wherein the peptide analogue has the formula (SEQ ID N° : 7):

Ac-D-Nal-D-pClPhe-D-Pal-Ser-A5-A6-A7-A8-Pro-D-AlaNH_2 (II')

in which :
- A5 is Tyr, HTyr, MeTyr, MeHTyr, NicLys or IprLys;
- A6 is (S)spirolactam-Pro, D-Arg, D-NicLys, D-IprLys, D-Cit, D-HCit or D-Asn;
- A7 is Leu, MeLeu, Npg or MeNpg;
- A8 is Arg, NicLys or IprLys.

Sub A8

55. The method according to claim 53 or 54 wherein the peptide analogue is selected from the group consisting of antide, [Npg^7]-antide, cetrorelix, [Npg^7]-cetrorelix, abarelix and [Npg^7]-abarelix.

56. The method according to one of claims 47 to 55 wherein the α-cyclodextrin derivative is selected from the group consisting of methylated α-cyclodextrin, hexakis(2,3,6-tri-O-methyl)-α-cyclodextrin, carboxymethylated α-cyclodextrin and phosphated α-cyclodextrin.

57. The method according to claim 56 wherein the α-cyclodextrin derivative is hexakis(2,3,6-tri-O-methyl)-α-cyclodextrin.

Sub A9

58. The method according to one of claims 47 to 57 for the treatment or prevention of breast cancer.

59. The method according to claim 58 which further comprises the sequential, parallel or over a period of time administration of at least one compound selected from the group consisting of an antiestrogen, an aromatase inhibitor and a C_{17-20} lyase inhibitor.

Sub A10

60. The method according to one of claims 47 to 57 for the treatment or prevention of prostate cancer or benign prostatic hypertrophy.

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61. The method according to claim 60 which further comprises the sequential, parallel or over a period of time administration of at least one compound selected from the group consisting of an antiandrogen, a 5α-reductase inhibitor and a C_{17-20} lyase inhibitor.

62. The method according to one of claims 47 to 61 wherein the peptide analogue is delivered to the gastrointestinal tract of the patient.

P19 lines 17-21

Sub A11

Add A12